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PRINCIPAL INVESTIGATOR: Dr. Craig D. Shriver, MD

CONTRACTING ORGANIZATION: The Henry M. Jackson Foundation for the Advancement of Military, Inc.
Bethesda, Maryland 20817

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14. ABSTRACT The Walter Reed National Military Medical Center Bethesda/Windber Clinical Breast Care Project will help lead the way in the 21 st century in the crusade against breast disorders. The project will utilize a multidisciplinary approach as the standard of care for treating breast diseases and breast cancer. This multidisciplinary model integrates prevention, screening, diagnosis, treatment and continuing care, but the project is further unique in the incorporation of advances in risk reduction, informatics, tissue banking and research. These efforts focus on decreasing the morbidity and mortality of breast cancer among American women.					
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**Comprehensive Reproductive System Care Program—Clinical Breast Care
Project (CRSCP-CBCP) Annual Report
COL Craig D. Shriver, M.D.;
Principal Investigator and Director**

I. Introduction

Objective/Hypothesis: Utilize our unique biorepository of well characterized biospecimens from a broad subset of patients with breast cancer and other breast diseases to broaden our knowledge of the etiology and pathology of breast disease. Leverage the technological advances in genomic and proteomic research to further our understanding of breast cancer through discoveries in molecular biology, pathway analysis and systems biology that can be readily translated in to the clinic.

Specific Aims

This project is structured around three major themes: clinically relevant molecular profiles, evaluation of genetic risk and tumor biology. These themes inform research across the five BC-TRCOE pillars: (1) Breast Cancer Risk Reduction; (2) Biorepository; (3) Focused Research (Genomics, Proteomics); (4) Biomedical Informatics; and (5) Clinical Care.

Study Design: The project utilizes a multidisciplinary approach for researching breast diseases and breast cancer. This multidisciplinary model integrates prevention, screening, diagnosis, treatment and continuing care, but the project is further unique in the incorporation of advances in risk reduction, biomedical informatics, tissue banking and translational research. The project is based on a Discovery Science paradigm, leveraging high-throughput molecular biology technology and our unique clinically well-characterized tissue repository with advances in biomedical informatics leading to hypothesis-generating discoveries that are then tested in hypothesis-driven experiments.

Relevance: The BC-TRCOE is the continuation of the Clinical Breast Care Project (CBCP) that has been ongoing for more than 11 years. Its uniqueness and relevance has been attested to by numerous world-class cancer experts, from the innumerable public and private presentations made by CBCP investigators over the years, as well as by the extensive publication record of CBCP researchers. CBCP has developed the world's largest biorepository of human breast tissues and biospecimens. CBCP has one of the few fully integrated genomic and proteomic molecular biology research programs in the nation devoted exclusively to research in breast diseases that is linked directly to the clinic and the patients (translational research).

Background

Breast cancer is the most common non skin-related malignancy among women in the western world. It accounts for one-third of all cancers diagnosed. Age is the single most important risk factor for the development of breast cancer, as incidence and mortality both increase with age. However, a significant number of breast cancers are diagnosed among young women. Each year, over 10,000 new breast cancer cases are detected in women under the age of 40. Over 90% of these occur among women aged 30-39 years and 8 women per 10,000 in this age group die from breast cancer every year. Breast cancer is the single leading cause of death in women aged 40-49 years. Despite the low absolute risk of breast cancer in women under 40 years of age, the incidence is increasing in this age group. The incidence in younger

women is probably underestimated based on the current understanding of the biology of breast cancer. Given the doubling time of most breast carcinomas a one centimeter breast cancer is estimated to have been *in situ* for a period of four to six years. Cancers identified in women age 40 to 45 originated at an age (> 40) when screening mammography would not have been recommended. Thus, given current screening recommendations, many breast cancers that develop in the fourth decade of life are not discovered by standard screening methods until the woman is older. The age-specific incidence for breast cancer among African American women is two times that of white women among those 30-39 years of age and the breast cancer mortality rate is nearly two times higher for African American women as compared to Caucasian women (12.8 versus 6.6 per 10,000 women, respectively). These differences have been attributed to significant ethnic and racial variations in the stage of disease at time of diagnosis, prevalence of adverse patient and tumor-related prognostic factors, and differences in provided cancer treatment. African American women are diagnosed with later stage disease and more aggressive tumors than white women accounting for the poorer overall survival among African American women with breast cancer. Reduction in ethnic and racial differences in breast cancer treatment outcome is a principal aim of modern day health care, and aggressive screening programs in young women aged 30-39 to detect disease at an early stage could assist in achieving this goal and improving cancer-related survival.

Hypothesis/Rationale/Purpose

The Walter Reed National Military Medical Center and Windber Research Institute have partnered in the Clinical Breast Care Project (CBCP) since its inception. This program has become a leader in the fight against breast disorders and cancer. Recognition of this leadership has prompted Congress to establish the CBCP as the Breast Cancer Translational Research Center of Excellence (BC-TRCOE), one of five centers so designated by Congress in 2008. The project utilizes a multidisciplinary bed-to-bench-to-bedside approach as the standard for treating and studying breast diseases and breast cancer. This multidisciplinary model integrates advances in risk reduction, prevention, screening, diagnosis, treatment and continuing care with cutting edge research incorporating advanced methods from biomedical informatics, tissue banking, high throughput biology and translational research. These efforts focus on decreasing the morbidity and mortality of breast cancer among American women.

The BC-TRCOE currently utilizes the facilities, resources and expertise of the Walter Reed National Military Medical Center (WRNMMC), the Windber Research Institute (WRI), the Windber Medical Center (WMC) and the Anne Arundel Medical Center (AAMC). The BC-TRCOE fosters a collaborative and collegial working relationship with its partners, other government agencies, academic institutions, commercial/industry leaders, and other non-profit organizations. The CBCP has a five pronged approach to the study and treatment of breast disease based on five interlocking pillars: **(1) Breast Cancer Risk Reduction; (2) Biorepository; (3) Focused Research (including: Genomics, and Proteomics Research); (4) Biomedical Informatics; and (5) Clinical Care.**

The overall purpose of the BC-TRCOE is to provide a balanced environment between the

two competing and yet complementary research paradigms of hypothesis-driven research and hypothesis-generating research, in a translational research organization that unites clinical capabilities (patients, nurses, clinicians) with research capabilities (genomics, proteomics, immunohistochemistry and whole genome DNA sequencing) to analyze molecular and developmental pathways that are central to the diagnosis and treatment of breast disease. The critical foundations to this approach are provided by the tissue biorepository and biomedical informatics platforms.

We believe that there are three broad areas where the BC-TRCOE stands poised to make major contributions to breast cancer research and its translation into clinical practice. These areas include the identification of molecular profiles of disease with high clinical relevance, deepening our understanding of the genetic risk of breast disease and the enhancement of our understanding of breast tumor biology. These three themes are supported by the five pillars of the BC-TRCOE. There is no doubt that our understanding of the biology of Breast Cancer in all of its various forms and manifestations remains incomplete. We believe that our high-value repository of biospecimens, our strong biomedical informatics infrastructure and our research base with strong internal and external collaborations puts us in an excellent position to make contributions to the understanding of breast disease that will have impact on the quality of life for breast cancer patients and their families.

Clinically Relevant Molecular Profiling: This is cross-cutting theme with clinical, risk assessment and basic research components. The primary focus of this theme is to evaluate the utility of existing molecular profiles that have relevance to risk assessment, diagnosis, prognosis and therapy in a clinical setting and to discover new profiles that can be evaluated in the clinic. Projects within this theme have well defined translational goals. The development of comprehensive and highly informative molecular profiles will be a foundation for the development and delivery of personalized/individualized medicine. A variety of research modalities will be used to identify these profiles including immunohistochemistry, gene and protein expression analysis and genetic profiling including Next Generation DNA Sequencing. Two major new initiatives are outlined below one involving the development and testing of clinically relevant immunohistochemical profiles for disease stratification and therapeutic guidance and the other using complete genomics sequencing of tumor and matched normal DNA to develop clinically relevant profiles that could aid in disease diagnosis, prognosis and therapy selection.

Genetic Risk: The rapid developments of high throughput genotyping and genomic sequencing of individuals has reminded the research community of the power of family studies in the assessment of genetic risk. Evaluating family risk and translating that into individual risk is the primary goal of this theme. There is both clear clinical relevance and a strong basic research component to this theme. Understanding the underlying biology of observed racial disparities in disease prevalence, presentation and outcome will also be a major part of this effort. The interaction of the theme with the Risk Reduction pillar of the BC-TRCOE and the number of projects outlined below that deal with research into the basis of the observed racial disparities in breast cancer morbidity and mortality point out the relevance of this theme to the overall goals of the BC-TRCOE.

Tumor Biology: A unique combination of resources and expertise put the BC-TRCOE in a strong position to further our understanding of the basic biology of breast disease including breast cancer. Many of the projects outlined in the Focused Research pillar address basic problems associated with tumor heterogeneity. The tumor microenvironment and stromal interactions, metastasis and recurrence, as well as the role of cancer stem cells and tumor evolution affecting the efficacy of treatment are emphasized. We firmly believe that a robust understanding of breast tumor biology is a key to the successful translation of the research preformed at the BC-TRCOE to the clinic.

II. Body

Ultimate Goals:

- Decrease morbidity and mortality of breast cancer among American women. The BC-TRCOE building upon the five pillars of the CBCP will help lead the fight against breast disorders.
- Continue to develop a comprehensive breast care center/system with a multidisciplinary team approach that enables health care providers to work towards the common goal of reducing the morbidity and mortality caused by breast disease.
- Empower women afflicted with breast cancer and other breast disorders, with the decision-making tools and an environment that enhances their quality of life and meets psychosocial needs of the patients and their families.
- To continue support and grow a world-class biorepository of biospecimens that enable research into diseases of the breast.
- Develop research facilities that drive world-class high-throughput translational research.
- Develop an integrated computational and biomedical informatics infrastructure with an integrated data warehouse that forms the foundation for analysis of research findings leading to new and actionable knowledge related to diseases of the breast.
- Empower the clinical staff with a physician decision support system incorporating our evolving understanding of breast cancer and other breast diseases from research both within and outside the BC-TRCOE

Pillar Specific Goals and Objectives:

1. Breast Cancer Risk Reduction:

Current research shows there are a number of risk factors that may influence the development of breast cancer. Identifying people with these risk factors and implementing closer surveillance and risk reduction techniques may detect cancer earlier. Earlier detection of breast cancer leads to better prognosis and outcomes. Calculations of risk are based on computer models extensively validated as accurate in identifying women at high risk. Genetic counselors can help individuals and families make decisions regarding testing. For those who do test positive for the BRCA1 or BRCA2 gene,

surveillance (mammography and clinical breast exams) can help detect the disease at an early stage. A woman who tests positive can also consider taking the drug tamoxifen, which has been found to reduce the risk of developing breast cancer by almost 50 percent in women at high risk. Clinical trials are now under way to determine whether another drug, raloxifene, is also effective in preventing breast cancer. The objectives for the Risk Reduction Pillar are:

- Identify the population of patients at above average risk for the development of breast cancer.
- Decrease this identified population's rate of breast cancer development.
- Analyze potential cost differential in the prevention of breast cancer development.
- Incorporation of newly identified markers of breast cancer risk into the assessment of breast cancer risk.
- Identify patients from families that might harbor mutations in the BRCA1 or BRCA2 genes and offer testing to identify these mutations
- Identifying families with unexplained high frequencies of breast cancer as potential research subjects

Hereditary breast cancer is suspected when there is a strong family history of breast cancer: occurrences of the disease in at least three first or second-degree relatives (sisters, mothers, aunts). Currently the only tests available are DNA tests to determine whether an individual in such a high-risk family has a genetic mutation in the BRCA1 or BRCA2 genes.

When someone with a family history of breast cancer has been tested and found to have an altered BRCA1 or BRCA2 gene, the family is said to have a "known mutation." Positive test results only provide information about the risk of developing breast cancer. The test cannot tell a person whether or when cancer might develop. Many, but not all, women and some men who inherit an altered gene will develop breast cancer. Both men and women who inherit an altered gene, whether or not they develop cancer themselves, can pass the alteration on to their sons and daughters.

But even if the test is negative, the individual may still have a predisposition to hereditary breast cancer. Currently available techniques can't identify all cancer-predisposing mutations in the BRCA1 and BRCA2 genes. Or, an individual may have inherited a mutation caused by other genes. And, because most cases of breast cancer are not hereditary, individuals may develop breast cancer whether or not a genetic mutation is present.

Genetic counselors can help individuals and families make decisions regarding testing. For those who do test positive for the BRCA1 or BRCA2 gene, surveillance (mammography and clinical breast exams) can help detect the disease at an early stage. A woman who tests positive can also consider taking the drug tamoxifen, which has been found to reduce the risk of developing breast cancer by almost 50 percent in women at high risk. Clinical trials are now under way to determine whether another drug, raloxifene, is also effective in preventing breast cancer.

The field of oncology/surgical oncology is an ever- changing one with new developments in both diagnosis and treatment. We propose to collect data from all patients in the WRNMMC Breast Translational Research Center determined to be at an elevated risk for developing breast cancer in order to assess risk factors in this population for developing the disease and track outcomes of preventive and therapeutic interventions. Analysis of outcome will include comparison of various treatment modalities/regimens with regard to efficacy, risks for failure, complications, and overall morbidity/mortality/survival. The patient population of WRNMMC can provide a significant number of patients to compare/contrast our findings with those of our civilian counterparts, specifically the Joyce Murtha Breast Care Center and the Pat and Lesly Sajack Breast Center at Anne Arundel Medical Center in Annapolis, Maryland. The database will also allow us to analyze breast cancer risk data to provide scientific-based evidence that will guide the general surgeon and medical oncologist in optimal care of the patient at an elevated risk for developing breast cancer.

Plan:

The risk Reduction Clinic at WRNMMC and at Joyce Murtha Breast Care Center (JMBCC) is a multi-disciplinary program designed to identify, counsel and manage women at high risk for breast cancer. Patients receive an in-depth personal and family health history by a world renowned medical oncologist.

Current research shows there are risk factors that may influence the development of breast cancer. Identifying people with these risk factors and implementing closer surveillance and risk reduction techniques may detect cancer earlier. Earlier detection of breast cancer leads to better prognosis and outcomes. Calculations of risk are based on computer models extensively validated as accurate in identifying women at high risk.

If patients are referred for genetic testing, as per the American Society of Clinical Oncology, counseling involves the following eleven points:

- Information on the specific test being performed
- Implications of positive and negative results
- Options for estimation without genetic testing
- Risk of passing a mutation to a child
- Technical accuracy of the test
- Possibility that the test will not be informative
- Fees involved in testing
- Risk of psychological distress
- Risk of insurance or employer discrimination
- Confidentiality issues
- Options for medical surveillance and screening following testing

It has been observed that healthy female relatives of individuals with ovarian or breast

cancer tend to exaggerate their risk of incurring either form of cancer and, thus, accurate risk assessment is essential to quality genetic counseling for breast cancer. Breast cancer genetic counseling serves the goal of helping women to analyze their own and their relatives' risk of developing breast cancer.

In BRCA screening, genetic counselors offer services in compiling family histories, personalizing epidemiology, and, more recently, conducting genetic testing to empower healthy women of families stricken by breast cancer to alter their lifestyles and healthcare to ensure avoidance or early detection of breast cancer. In addition, breast cancer victims and healthy members of a single family can enable accurate screening of female family members by obtaining a sequence of their BRCA genes. Detection of a familial BRCA mutation in individuals outside of the Ashkenazi Jewish population requires time-consuming genetic analysis of a large number of affected and unaffected family members in order to identify the specific BRCA mutation for a particular family.

In addition to a dedicated medical oncologist who sees patients who may be at high risk for breast cancer, this program employs a full time Genetics Clinical Nurse certified by the Genetic Nursing Credentialing Committee. She manages a population of patients identified as being at high-risk for breast cancer. She implements detailed family pedigree analyses and statistical tools such as the Gail model to evaluate patients in-depth for potential chemoprevention strategies and participation in genetic, preventive and surveillance research projects in conjunction with in-house medical oncologists and /or NCI researchers. She provides initial genetic evaluation and pre-test counseling for patients referred for consideration of breast cancer genetic testing. She provides in-depth post test counseling and long term follow up in conjunction with appropriate physician specialists and genetic counselors. Counseling for patients at high risk for breast cancer may include prophylactic mastectomy, oophorectomy, salpingectomy and Tamoxifen. Tamoxifen (Nolvadex®) is a drug that interferes with the activity of estrogen, and has been used for almost 10 years to reduce the risk of breast cancer in women who are at increased risk of developing breast cancer.

Testing positive or negative for a BRCA mutation is simply a risk assessment, not a certainty of experiencing or avoiding, respectively, breast cancer. Individuals with a BRCA mutation have an 80% risk of developing breast cancer by age 80. Therefore, 20% of BRCA mutation carriers never develop breast cancer. A first-degree relative of a carrier who tests negative for the mutation has the same breast cancer risk as women of the general population, namely 11%.

Dr. Raymond Weiss, medical oncologist, saw 292 patients at high risk for breast cancer between 2 April 2012 and 31 March 2013 at Walter Reed National Military Medical Center Bethesda. He additionally saw 9 walk-ins and conducted 114 tele-conferences for consultation.

2. Biorepository:

Although there have been remarkable improvements in breast cancer diagnosis and management, most of the complex molecular mechanisms associated with the onset, progression and/or severity of breast cancer are still not well understood. As part of the Breast Translational Research Center (BC-TRC) we carry out molecular, biochemical and histological analysis of breast tissue and/or blood and blood components from breast cancer patients to provide insights into the molecular mechanisms that may be relevant in the development of breast cancer and breast diseases. To achieve this aim, a large supply and a wide variety of good quality tissue samples are needed. Unfortunately, good quality donor breast tissue is extremely scarce and when available is often not backed by a comprehensive medical history and/or is not a good representation of the target population or study area. The non-availability of a steady and consistent supply of good quality tissue limits the systematic analysis of tissues and negatively impacts the generation of biologically useful information in research laboratories and by extension negatively impacts new findings that benefit clinical practice. The objective of this project is therefore the acquisition and banking of breast tissue, lymph nodes, serum/plasma and other blood derivatives from informed and consenting donors.

- Collect and store a broad spectrum of biospecimens from every patient undergoing a breast biopsy and/or breast surgery at WRNMMC, WMC, AAMC, and our affiliated hospitals, that consent to participate in BC-TRC IRB-approved protocols.
- Collect and store biospecimens (blood) from women who are free of breast disease who consent to participate in BC-TRC IRB-approved protocols to act as controls.
- Utilize the power of this extensive biorepository as a major resource for breast disease research.
- Leverage the BC-TRC biorepository to maximize the utilization of the repository, with BC-TRC leadership approval, for the overall benefit of breast cancer patients and research, as able and appropriate.
- Participate in national/international projects that can benefit from resources of the BC-TRC biorepository.

Figure BB-1 shows the cumulative patient accrual into the CBCP protocols since 2002. These patients, who have been recruited and consented into the CBCP protocols at WRAMC, WRNMMC, AAMC, JMBCC and other participating CBCP clinical intake sites are the foundations of the translational research that has occurred within the CBCP and which will continue in the BC-TRCOE. From these patients we have collected and stored in our biorepository over 51,849 biospecimens (**Figure BB-1**) donated by 5,977 fully consented subjects to our IRB approved tissue and blood protocols. (**Figure BB-2**)

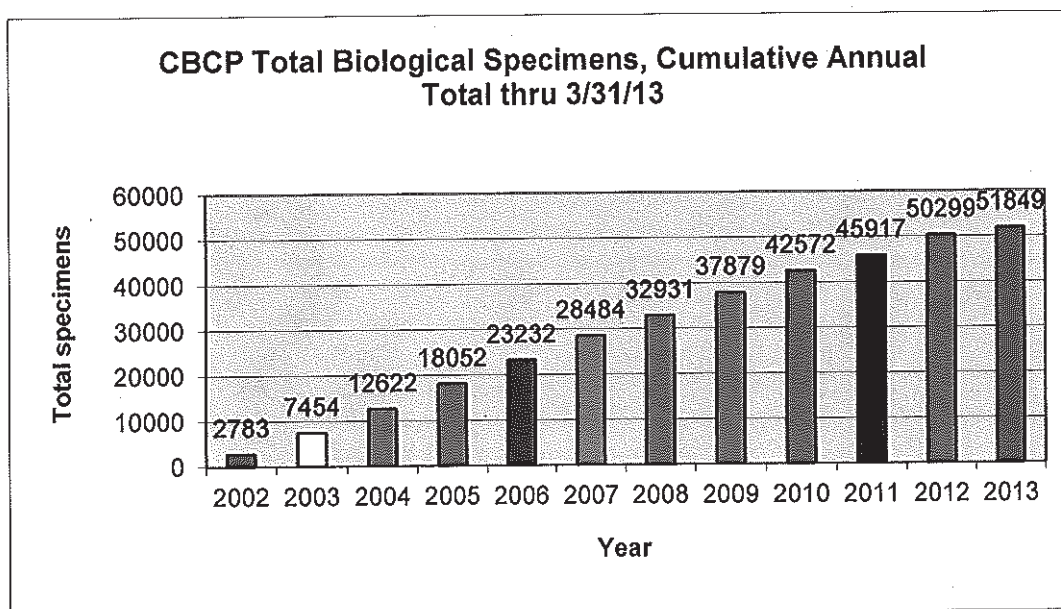


Figure BB-1. Total biospecimens collected and banked by the biorepository.

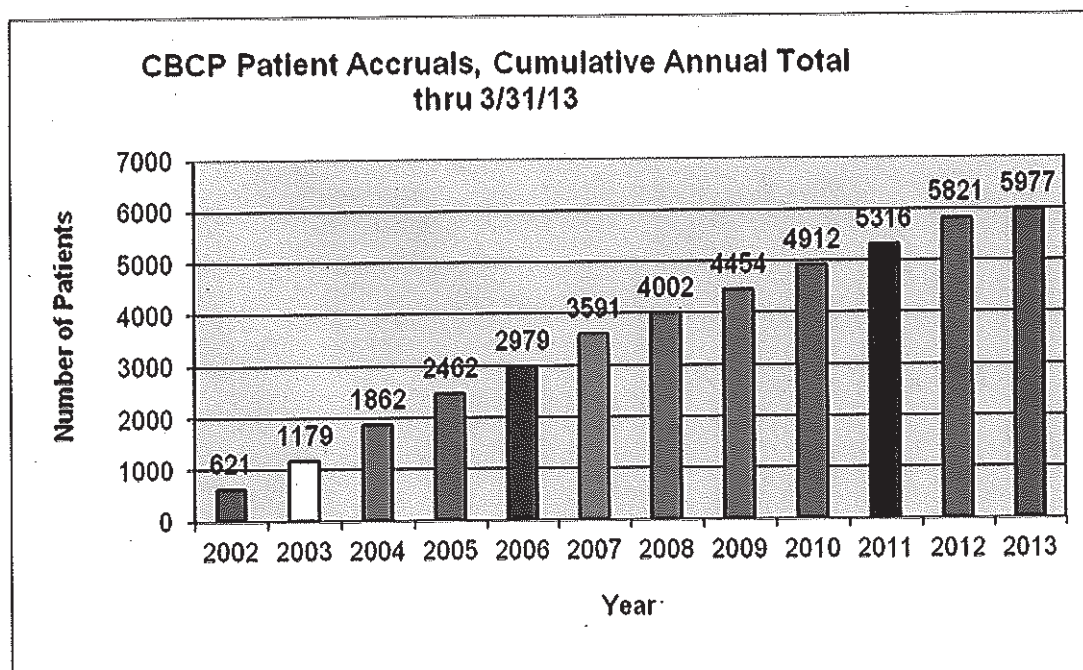


Figure BB-2 Cumulative patient accruals into CBCP protocols since 2002.

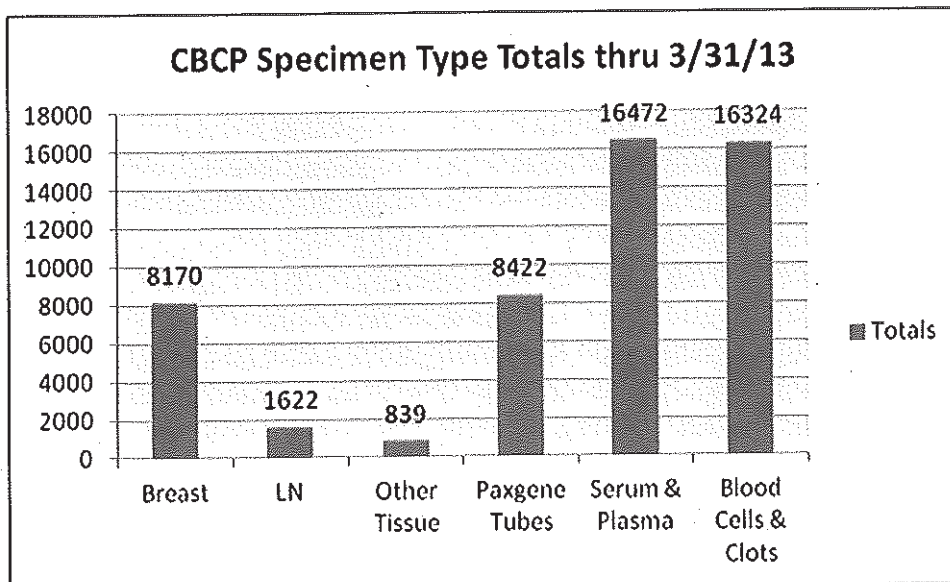


Figure BB-3. The numbers and types of biospecimens collected by the CBCP

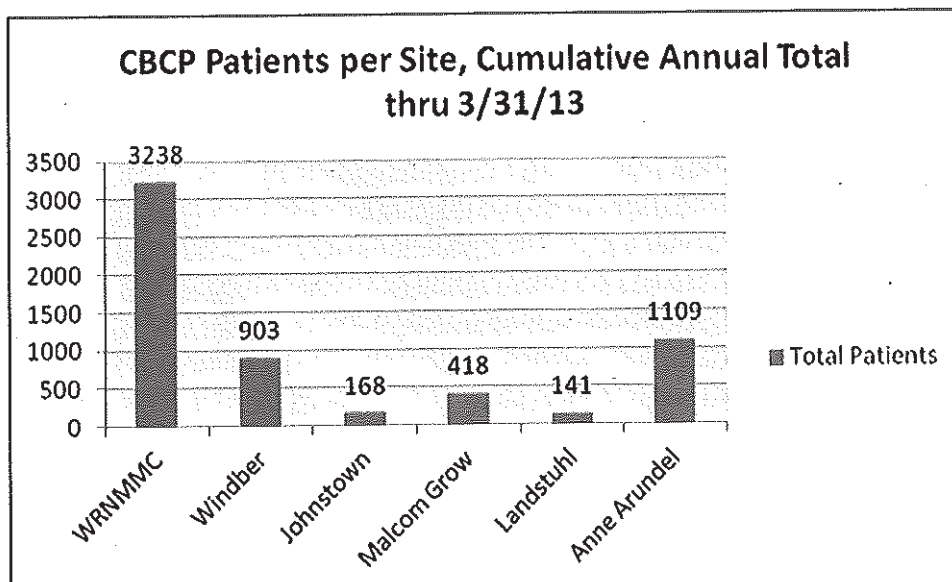


Figure BB-4. Numbers of patient recruited to CBCP protocols at various partner sites.

These specimens represent a broad spectrum of tissues, blood and blood products (Figure BB-3) that are not only a unique and valuable resource for the BC-TRC but are also the substrates for our translational research program. Along with the biospecimens that have been collected from CBCP participants, each consented patient also provides nearly 800 field of demographic, medical, life and family history data as well as complete pathology data on donated tissues. The collection of tissues that the BC-TRC inherits from the

CBCP is even more valuable because of this rich annotation. Patients have been recruited from a number of partnering clinical intake sites over the history of the CBCP (**Figure BB-4**). At the start of the BC-TRC the active partners are WRAMC, the Joyce Murtha Breast Care Center in Windber, PA, and the Anne Arundel Medical Center in Annapolis, MD.

3. Focused Research (including: Genomics and Proteomics Research):

The research pillar of the BC-TRCOE focuses on the translational research program involving the clinical programs at Walter Reed National Military Medical Center, the Joyce Murtha Breast Care Center, the Comprehensive Breast Center at AAHS and the genomic and proteomic analysis carried out at the Windber Research Institute.

The following is a description of the projects that make up the Focused Research Pillar of the BC-TRC. This includes both ongoing and new projects. Major new initiatives include a major project that will generate complete genomic DNA sequence from breast cancer cases. Another new initiative will utilize immunohistochemical to generate clinically relevant profiles of breast tumors to better stratify the disease in terms of prognosis and treatment options.

Genomics: Utilize high-throughput and translational research in a unique Discovery Science environment to include but not be limited to:

- DNA analysis with genotyping studies, Copy Number Variation (CNV), gene sequencing and whole genome sequencing
- RNA/cDNA micro arrays, to identify expression level differentials across the entire spectrum of breast disease and from cancer specimens of all stages and types, as well as the accompanying lymph nodes and metastatic deposits, and blood.
- Measure epigenetic changes associated with disease
- Study molecular differences between breast tumors from African American and Caucasian women as the identification of such differences will allow for the development of more effective therapies that will improve outcomes in African American women with breast cancer.
- Perform whole genome DNA sequencing on DNA from 40 or more cases of breast cancer.
- Using state-of-the-art 3D cell culture techniques and modern approaches to the study of cancer cell biology, study the mechanisms of cell invasion, migration and ultimately metastasis in breast cancer cell lines.
- Use our unique collection of breast cancer biospecimens to characterize microRNA (miRNA) expression in breast cancer progression and metastasis.
- Identify genetic changes in low- and high-grade breast tumors to improve our understanding of the evolutionary process of breast cancer and to identify a protein signature that can discriminate low- from high-grade breast tumors, allowing for more accurate diagnosis and risk assessment.
- Use our unique collection of breast cancer biospecimens to characterize molecular

signatures that can differentiate primary breast tumors with and without metastatic potential, as well as between primary tumors and subsequent metastases.

- Improve our understanding of the molecular changes associated with HER2 amplification and over-expression to allow for more precise diagnosis of HER2+ patients and development of customized treatment options in patients with HER2+ breast cancer.
- Study the role of matrix metalloproteinases in breast cancer with the goal of developing diagnostic and prognostic marker of breast cancer based on expression of MMPs and polymorphisms in MMPs.
- Identify molecular alterations in the breast tumor microenvironment that contribute to tumorigenesis and which may lead to improved methods of breast cancer prevention and treatment.
- Use our unique collection of breast cancer biospecimens to study angiogenesis and lymphogenesis in different grades of DCIS and IDC.

Proteomics: Through collaboration with world class partners, utilize high-throughput and translational research in a unique Discovery Science environment to include but not be limited to:

- Identify protein signatures associated with the development and progression of pre-malignant breast disease to improve our understanding of the biologic processes involved in early breast disease development and progression and to drive the development of personalized therapeutics for breast disease.
- Mass spectrometer pattern analysis and protein identification,
- Identify protein expression level differentials across the entire spectrum of breast disease and cancer specimens of all stages and types, as well as the accompanying lymph nodes and metastatic deposits, serum and blood
- Use Accurate Mass Tag (AMT) technology to assess protein expression changes in tumor tissues
- Search for novel protein biomarkers, individual or pattern.
- Store all this expression data in a data warehouse where it can then be utilized for biologic pathway development and in-silico biology research for hypothesis-driven research.

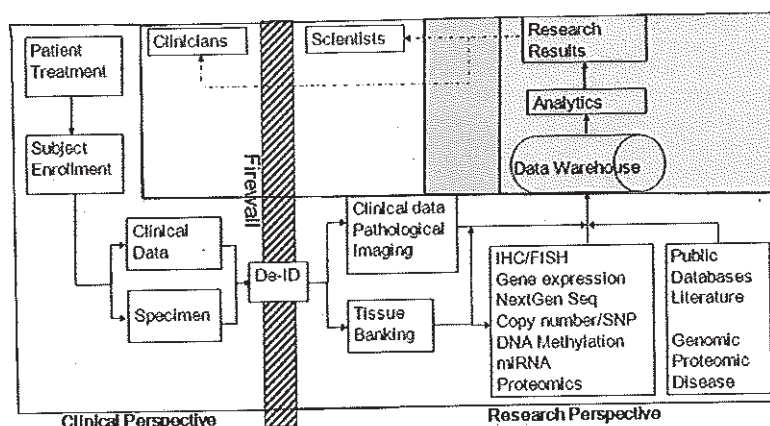
Collaborative Research: We have established a number of collaborations over the last several years that leverage the talents and resources of the BC-TRCOE to address research areas that would not have been possible using only our local resource base.

- Conduct quantitative analysis of therapy relevant proteins by immunohistochemistry within various subclasses of breast cancer to provide better patient selection into clinical trials for targeted and combination therapies.
- Perform affiliated translational laboratory research in support of the main expression profiling and biomarker discovery goals of the BC-TRCOE research laboratories.
- Develop alliances with other research organizations and entities and carry out project-supported research in support of same. Currently we have established

collaborations with the Pacific Northwest National Laboratory, Vanderbilt University. The Institute for Systems Biology, the Thomas Jefferson University, the MDR Global, etc.

- Collaborate with the NCI/NHGRI TCGA (The Cancer Genome Atlas) project to study the genomics of breast cancer.

4. Biomedical Informatics:



Biomedical Informatics focuses on the management and utilization of biomedical information, and our view of its role in translational research is shown on the left figure. From the data flow point of view, it involves data collection and generation, where data tracking is needed

(light blue). Cleaned data are then centralized in the data warehouse (light green), and subject to data analysis and mining for knowledge generation which is then presented to research scientists and clinicians to complete the two-way cycle of translational research (light yellow which partially overlaps with the data warehouse section).

As one of the original five pillars of the Clinical Breast Care Project, the Biomedical Informatics (BMIX) Group has become one of the foundations of the BC-TRCOE. The primary function of the BMIX team is the development and implementation of an infrastructure that supports the acquisition, storage, and maintenance of the clinical and molecular data generated by the Center. The successful accomplishment of this goal enables the development, implementation and support of the tools for data analysis that are necessary to achieve the research goals of the BC-TRCOE. The activities of this group requires that it both supports the research activities of the Center as well as carrying out research into new algorithms and methods that can lead to novel discoveries based on the unique resources, and data generated by this program. These functions are critical to meeting the translational research goals of the BC-TRCOE.

- Develop a comprehensive QA program and aid in SOP development for data collection and generation to ensure acquisition of high quality of data.
- Develop and support a robust laboratory information management system to ensure proper tracking of data acquisition.
- Develop and implement a clinically relevant and laboratory research-linked prospective, longitudinal computerized data warehouse to support translational research and ultimately support physician decision making
- Develop an analytical system including developing specific algorithms for

integrative data analysis and mining, and deploying existing applications and algorithms to ensure execution of data analysis, mining, and modeling.

- Develop a breast knowledgebase to support clinical and research activities in BC-TRCOE.
- Develop other needed infrastructure to support the activities in all other BC-TRCOE pillars.
- Incorporate the rapidly growing public genomic and proteomic datasets related to breast cancer into our data warehouse to be able to mine the combined data sets for the generation of new hypotheses regarding breast cancer development, progression and treatment

5. Clinical Care:

This pillar of the BC-TRCOE is the foundation upon which all the success of our endeavors rests. Without patients enrolled in our biospecimen repository protocols, there would be no translational research center. These patients come from the clinical care environment. Since its inception in 2000, the CBCP (now the BC-TRCOE) has had as a priority, the development and staffing of the core clinical centers at Walter Reed National Military Medical Center, the Joyce Murtha Breast Care Center in Windber, PA and at our newest site, the Pat and Lesly Sajack Breast Center at Anne Arundel Medical Center in Annapolis, Maryland, that, under the direction of Lorraine Tafra, MD sees more than 500 newly diagnosed cases of breast cancer each year. The objectives of the Clinical Care Pillar are:

- Provide state of the art clinical care and treatment of patients seen in the Breast Cancer Translational Research Center at Walter Reed National Military Medical Center Bethesda.
- Decrease the negative psychological impact on the patient of having an evaluation or treatment intervention for breast disease by utilizing objective measurement instruments to longitudinally assess the patient's psychological response to evaluation and intervention, and base modifications of these procedures on those results.
- Create and maintain an environment (medical, physical, psychological) conducive to the multiple needs of the patient undergoing breast disease evaluation / treatment.
- Recruit patients into the various BC-TRCOE protocols to obtain the clinical data and biospecimens needed to meet the BC-TRCOE translational research goals.

At each center the Staff is dually trained as clinical/research providers, to seamlessly integrate the need for a strong research focus in the clinical center with the requirement to provide state-of-the-art clinical care to the patients.

The care of our patients is provided by Physicians, Advance Practice Nurses (Nurse Practitioners) and Certified Breast Nurse Navigators with all personnel having the dual responsibility of clinical care and research. The Walter Reed National Military Medical

Center, Joyce Murtha Breast Care Center and Pat and Lesly Sajack Breast Center at Anne Arundel Medical Center in Annapolis, Maryland, are state of the art facilities.

WRNMMC Breast Care Rehabilitation Clinical Research Program

Since 1999 the National Naval Medical Center (now Walter Reed National Military Medical Center) Breast Care department has utilized a Prospective Surveillance Model (PSM) of rehabilitation care for women with breast cancer. The PSM provides ongoing education and evaluation of women before, during and after breast cancer treatment. Interval assessment of function, strength, mobility and limb volume is an effective mechanism to identify impairments early and introduce treatment when the impairment is in a less severe state. This model has been studied in an ongoing clinical trial (NCT00513838) <http://clinicaltrials.gov/ct2/show/NCT00513838> and demonstrates significant improvement in overall function and quality of life among breast cancer survivors.

The model is recognized as an emerging standard of care in both the national and international communities. http://www.washingtonpost.com/national/health-science/walter-reed-national-military-medical-center-tests-cancer-rehabilitation-model/2011/10/03/gIQAnu4daL_story.html

The PSM model will be featured in an upcoming supplement to the journal Cancer. A full supplement will be dedicated to highlighting the PSM and the evidence to support the model and it's components as a new standard of care in breast cancer.

The Multidisciplinary Conference

At the Walter Reed National Military Medical Center, we expect to see approximately 10,000 patients per year and will diagnose approximately 200 plus new breast cancers per year.

The Multidisciplinary Conference occurs every Thursday and the purpose of this day is to Provide an opportunity for the newly diagnosed breast cancer patient to meet all the providers that comprise the interdisciplinary breast care team. Providers include a breast surgeon, a medical oncologist, a radiation oncologist, a psychologist and /or social worker, nurse navigators/case managers, a physical therapist, and a plastic surgeon. Each specialty has individual private appointments to assess and evaluate each patient who, with significant others of their choice, is given a private room for the day. The benefit of the Multidisciplinary Conference Day is a one day visit to see all the various providers instead of having individual appointments spread over several days or weeks. This allows us to educate, facilitate and coordinate a comprehensive breast treatment plan for the patient that maximizes treatment options and streamlines patient care in a patient-focused environment.

It also allows us to discuss the various research protocols with patients and, if they agree, obtain informed written consent and complete, with the assistance of a research nurse, an extensive questionnaire that captures more than 500 fields of clinical data.

The breast care team assembles and conducts an interdisciplinary conference to discuss each patient's case, resulting in a comprehensive treatment plan built on a team consensus. The results of the conference are then reviewed with the patient/family and time is provided to clarify and ask questions.

In an article entitled "*Hidden in Plain View – Integration of Effective Patient Partnerships with Evidence Based Medicine in the Military Health System –The Walter Reed Army Medical Center Clinical Breast Care Project*" the TEMPLATE day is described by the following quote "This method of physician communication and consensus avoids conflicting messages to the patient and allows for the best evidence-based approach. The literature supports the notion that a group decision is superior to sequential individual ones. Staff and patient satisfaction, stability of staff retention, and continuous improvement attitude, creates optimal outcomes in a safe, high quality, and supportive, attractive physical environment. As the Program Director NCC General Surgery Residency Director, clearly COL Shriver leads by example and has an impact on physicians during their graduate medical education by experiencing how idealized care can be operationalized in a military setting. This model of care should certainly be considered as the National Capital Area moves forward with the merger of Walter Reed Army Medical Center with the National Naval Medical Center and becomes the Walter Reed National Military Medical Center (WRNMMC) in 2011."

Military Relevance:

Breast cancer is the most common non-skin cancer in women. It is the single greatest cause of cancer deaths among women under 40, and is a significant cause of mortality for women in the United States Armed Forces. Breast cancer mortality among women <50 years accounts for >40% of years of life lost due to this disease. The economic, social and emotional costs to families are far greater when a young woman dies than when an older woman dies of breast cancer. The more aggressive nature of the disease in young patients along with the attendant costs underscores the importance of early detection of breast cancer in young women. Breast cancer is a curable disease if it is detected early; as such early detection is related to survivorship, cost of treatment and quality of life for the affected woman.

The majority (>90%) of women in active military service are < 40 years of age. The Department of Defense (DOD) with its high percentage of young women and its commitment to health care is particularly concerned about breast cancer. When discovered at a later stage, treatment of breast cancer is expensive, aggressive and results in considerable disruption to the woman's ability to contribute to society. Cost and disruption to life are considerably less when the carcinoma is discovered at an earlier stage. Furthermore, the DOD has a high percentage of African-American (~40%) and Hispanic (~10%) women. Death rates from breast cancer tend to be particularly high in these ethnic groups owing in part to later stage of detection and to the more aggressive nature of breast cancer in these groups.

The active duty military force is approximately 20% female. Most of these service

members are in the age range (30-40 years) where routine screening for breast cancer consists only of clinical breast examination. Both mammography and clinical breast examination have a very poor accuracy in the young active duty force in determining which breast abnormalities require treatment, and which are benign and can be left alone. The immense scale and impact of this problem for the military can be assessed by the fact that there were over 2,000 cases of breast cancer diagnosed in active duty service members over the last ten years (source: ACTURS DoD Tumor Registry data). Furthermore, there were over 8,000 unnecessary breast biopsies done on active duty women during this time because it takes 4 breast biopsies of normal non-cancerous lesions to find each individual breast cancer. Hence, women often need to take lengthy amounts of time off from duty in order to undergo multiple tests leading up to the biopsy as well as time off from duty because of the biopsy itself. This translates into approximately 10,000 weeks, or 30 person-years, of time lost in the evaluation of normal, benign breast lesions in active duty service members. This would be unacceptable for any other healthcare issue, and should be so for this one. Unfortunately, at the present time there is no screening tool available to diagnose breast cancer in the early, curable stages for women under the age of 40, who make up the vast majority of women in military uniform.

III. Key Research Accomplishments

Breast Cancer Translational Research Center of Excellence (BC-TRCOE) Congressional Special Interest (CSI) FY10 Statement of Work

Task 1: Support the analytical system for integrative data analysis and mining by providing quality assurance of clinical data obtained through patient interview, utilizing the Data Correction Utility (DCU) to correct and update data warehouse contributing to the development of a breast knowledgebase to support clinical and research activities in BC-TRCOE.

Task 2: Identify and counsel no less than 100 patients at high risk for development of breast cancer, and employ risk reduction strategies.

Task 3. Provide administrative support for the Risk Reduction program with nursing support for medical oncologist, consumable supplies, computer equipment and computer upgrades.

Task 4: Accrue over 500 patients annually to the "core" BC-COE protocols through consenting patients in the main BC-COE clinical sites.

Task 5: Perform focused research as outlined below on the biospecimens and clinical data collected under the BC-COE Core protocols including global expression analysis of the DNA, RNA, and Protein features and including targeted research into genomic

analysis of Stages I, II, and III breast cancer, DCIS, LCIS, and pre-malignant neoplasia and cell biology of breast cancer. Present findings in peer-reviewed national meetings and publications.

Task 6: Develop an analytical system for integrative data analysis and mining, and develop a breast knowledgebase to support clinical and research activities in BC-COE.

Task 7: Provide the scientific staff memberships in professional organizations, subscriptions to peer reviewed journals and publications, and graphic support for presentations on scientific findings at national meetings.

Key Research Accomplishments (continued)

- Further enhancements have been made to the database and data warehouse system that CBCP has developed for last five years, to integrate the clinical, molecular, pathologic, and biorepository aspects of CBCP translational research. The data warehouse and the On-Line Analytical Processing tool as the interface have proven to be a powerful tool in supporting scientific research at WRI and WRAMC and the underlying patient centric data model is being modified to support other types of disease.
- Gene expression difference have been found between African American women and Caucasian American women that may lead to insights into the differences in breast cancer severity seen between these populations. Recently we generated gene expression data from both tumors and non-malignant tissues from AAW and CW. 18 genes were differentially expressed in tumors and 13 genes in non-malignant breast specimens, including PSPHL, SOS1 and CRYBB2, which are differentially expressed in both tumors and non-malignant tissues.
- The Biomedical informatics core has continued development of the patient centric data model, enhanced tools for microarray data QA, and further analysis of breast disease co-occurrence.
- Numerous QA issues have been identified and entered into the QA Issue Tracking system for Walter Reed. At the same time a significant number of issues we previously reported have now been resolved by working with team at Walter Reed.
- We have published the results of an evaluation of Allelic Imbalance in non-neoplastic diseases, concluding that ADH and CCH are in fact, genomically naive and that the multitude of studies that have evaluated pre-neoplastic lesions from breasts with invasive breast tumor cannot represent the status of pure early lesions.

- Copy number evaluation is being performed on fresh frozen genomic DNA samples from women with breast cancer, and a variety of pathological classifications using Affymetrix 500K SNP chips. Copy number and LOH analysis is being performed using Affymetrix genotyping console. Data have been presented in several different forums.
- In collaboration with Pacific Northwest Laboratory (PNNL) using the previously developed Accurate Mass Tag data base for proteins expressed in breast tissue we have examined breast tumors for the proteins that are markers of metastasis to lymph node.
- The current Clinical Laboratory Workflow System (CLWS) for tracking the information of clinical data and biospecimen collection and processing is gradually losing of the capability to support our needs and we have decided to develop a system to replace it.
- In this report period, we identified matched data elements in the MeSH, and the corresponded MeSH IDs have been extracted and put onto metadata files. Not all our data attributes are matched in MeSH. During this process, we discovered that some hierarchical structures in our data model could be rearranged. Such rearrangements have been implemented and the revised data model has been deployed in the Data Warehouse for Translational Research as of January, 2012.
- In this report period, we identified the needs to model new data elements (such as BRCA1/2, site, etc.). The workflows for loading the data for these elements have been developed and implemented. The next step is to incorporate these modules into the whole data model.
- The Data Correction Utility continues to serve its purpose, and 109 Core/Follow up and 19 Pathology Checklist corrections have been made in the DW4TR through the DCU.
- As an effort to continue developing the DW4TR, we started to drastically expand the sample-centric experimental modules to host other molecular data than what have already been covered, namely IHC, FISH, and gene expression microarray.

Complimentetary Activities supported by separate funding:

- Work continues on a 6.7 million dollar Komen Promise grant awarded to Hallgier Rui of Thomas Jefferson University in 2009. On behalf of the Clinical Breast Care Project at Walter Reed Army Medical Center, the Henry M. Jackson Foundation is committed to participate as a consortium collaborator on this grant submission: **"Therapy-relevant Stratification of Breast Cancer Patients: Integrating Pathology and Biomarker Analyses"** As for the progress, Aim 1 of the grant involves the block and clinical data collection efforts and most of our work has been directed at this activity. The CBCP planned to submit approx. 500

cases. To date, we have collected blocks on 263 cases and have completed the clinical data forms on 196 cases. Of these 196 forms, we have performed a Quality Control check on 61 of them and sent them to the bioinformatics team for data entry testing. From the CBCP perspective, the next few months will also be directed at collecting blocks on the remaining 237 cases (approx.) and completing the completion and QC of all data forms.

- **The Cancer Genome Atlas project for NCI:**

We have been shipping biospecimens to the TCGA (The Cancer Genome Atlas) since late 2010. We have sent 97 cases (tumor and normal samples) of which 86 have passed the QA/QC processes of the project. We are in the process of collecting clinical data (enrollment, pharmaceutical therapy and radiation therapy data) on these cases and have entered the information in OpenClinica. These cases along with approximately 700 other samples are undergoing analysis. CBCP scientists have been part of the team analyzing the exome sequences, copy number variations, gene expression, micro RNA content, DNA methylation analysis and the results of reverse phase protein arrays from these samples. The study, a collaborative effort funded by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both part of NIH, was published online Sept. 23, 2012, and in print Oct. 4, 2012, in the journal Nature. "TCGA's comprehensive characterization of their high-quality samples allows researchers an unprecedented look at these breast cancer subgroups," said NIH Director Francis S. Collins, M.D., Ph.D. The TRC/CBCP had 11 authors on this prestigious publication.

IV. Reportable Outcomes

The CBCP Research Protocols Samples Collected and number of subjects recruited by site for the period 02 April 2012 to 31 March 2013 are as follows:

Total Samples Collected from 4/2/12 – 3/31/13

- Blood - 3498
- Breast tissue - 973
- Lymph Node - 25
- Other - 168

Total Patients enrolled from 4/2/12 – 3/31/13

- WRNMMC - 141
- JMBCC Windber - 96
- AAMC - 264

Total enrolled – 501

Total samples collected – 4,664

Publications, Abstracts and Presentations 02 April 2012 – 31 March 2013

Rummel S, Varner E, Ellsworth R, Shriver C. "Evaluation of BRCA1 mutations in patients with Triple Negative breast cancer." AACR, Chicago, IL, 31 Mar – 4 Apr 2012.

Rummel S, Shriver CD, Ellsworth RE. "Evaluation of the association of the ABO blood group SNP rs505922 with breast cancer phenotypes." AACR, Chicago, IL, 31 Mar – 4 Apr 2012.

Field L, Deyarmin B, van Laar R, Shriver C, Ellsworth R. "Evaluation of the association of the ABO blood group SNP rs505922 with breast cancer phenotypes." AACR, Chicago, IL, 31 Mar – 4 Apr 2012.

Rummel S, Valente AL, Kane JL, Ellsworth DL, Shriver CD, Ellsworth RE. "Genomic instability of the breast tumor microenvironment: stromal alterations or technological artifact?" AACR, Chicago, IL, 31 Mar – 4 Apr 2012.

Field L, Deyarmin B, van Laar R, Shriver C, Ellsworth R. "Identification of Gene Expression Profiles Associated with Different Types of Breast Adipose and Their Relationship to Tumorigenesis." AACR, Chicago, IL 31 Mar – 4 Apr 2012

Rummel SK, Valente AL, Kane JL, Ellsworth DL, Shriver CD, Ellsworth RE. "Genomic instability of the breast tumor microenvironment: stromal alterations or technological artifact?" *Cancer Research*, Apr 15, 2012; 72(8)sup 1. doi: 10.1158/1538-7445.AM 2012-3037.

Greer LT, Rosman M, Mylander C, Kovatich AJ, Hooke JA, Woodward J, Campbell JL, Wareham J, Liang W, Buras RR, Shriver CD, Tafral L. "Should Immunohistochemical Markers be Performed on the Surgical Specimens Rather than the Core Needle Biopsy in Breast Cancer Patients?" ASBS, Phoenix, AZ, 2-6 May 2012.

Greer L, Rosman M, Mylander WC, Wareham J, Campbell JL, Kovatich A, Hooke JA, Woodward J, Liang W, Buras R, Shriver CD, Tafral L. "Loss of Concordance in Immunohistochemical Markers Between Core Needle Biopsy and the Surgical Specimen in Heterogeneous Breast Tumors." ASBS, Phoenix, AZ, 2-6 May 2012.

Iida J, Dorchak J, Clancy R, Hu H, Mural R, Shriver C. "Role for wnt/beta-catenin pathways for facilitating triple-negative breast cancer migration and growth." Gordon Research Conference, Andover, NH, 7-13 Jul 2012.

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Greer, LT, Rosman M, Mylander CW, Hooke JA, Kovatich A, Sawyer K, Buras R, Shriver CD, Tafral L. "Does Breast Tumor Heterogeneity Necessitate Further Immunohistochemical Staining on Surgical Specimens?" Association of Women Surgeons (AWS) 6th Annual Starr Poster Competition, Chicago, IL, 30 Sep 2012

Iida J, Dorchak J, Lehman JR, Clancy R, Luo C, Chen Y, Somiari S, Ellsworth RE, Hu H, Mural R, Shriver CD. FH535 inhibited migration and growth of breast cancer cells." *PLOS ONE*, Sept 2012; 7(9) e44418. doi:10.1371/journal.pone.0044418.

Greer LT, Rosman M, Mylander C, Wareham J, Campbell JL, Hooke JA, Kovatich AJ, Shriver CD, Tafral L. "Should Immunohistochemical Markers be Performed on Axillary Lymph Node Metastases in View of the Lack of Concordance Between The Primary Tumor and Axillary Lymph Node Metastases?" American College of Surgeons 98th Annual Clinical Congress, Chicago, IL, 30 Sep – 4 Oct 2012.

Ellsworth RE, Shriver CD. "Demographic differences in African American compared to Caucasian women with luminal A breast cancer." AACR Science of Cancer Health Disparities, San Diego, CA, 27-30 Oct 2012.

Mural R. "Prestigious Journal to Publish Collaborative Breast Cancer Research." Article for HJF SCOOP Oct 2012.

Rummel SK, Valente AL, Kane JL, Ellsworth DL, Shriver CD, Ellsworth RE. "Genomic instability of the breast tumor microenvironment: stromal alterations or technological artifact?" *Mol Cancer Res*, 2012 Oct 4; 230388135.

Valente AL, Rummel S, Shriver CD, Ellsworth RE. "CDH1 mutations in patients with lobular carcinoma of the breast." ASHG, San Francisco, CA, 6-10 Nov 2012.

Rummel S, Shriver C, Ellsworth R. "Evaluation of BRCA1 mutations in patients with family history of breast cancer." ASHG, San Francisco, CA, 6-10 Nov 2012

Field L, Deyarmin B, van Laar R, Hooke J, Shriver C, Ellsworth R. "Molecular characterization of breast tumor-associated adipose." SABCS, 4-8 Dec 2012.

Ellsworth R, Valente A, Shriver C. "The effect of HER2 expression on luminal A breast tumors." SABCS, San Antonio, TX, 4-8 Dec 2012.

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Luo C, Iida G, Chen Y, Dorchak J, Kovatich AJ, Mural RJ, Hu H, Shriver CD. "Higher gene expression of CSPG4 in the basal-like subtype of invasive breast cancer and its negative association with lymph node metastasis." SABCS, San Antonio, TX, 4-8 Dec 2012.

Luo C, Chen Y, Kovatich AJ, Hooke JA, Kvecher L, Shriver, CD, Mural RJ, Hu H. "P53 gene and protein expression patterns in human invasive breast cancers are correlated with its mutation status." SABCS, San Antonio, TX, 4-8 Dec 2012.

Dorchak J, Iida J, Clancy R, Luo C, Chen Y, Hu H, Mural RJ, Shriver CD. "FH535 inhibited migration and growth of breast cancer cells." SABCS, San Antonio, TX, 4-8 Dec 2012

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Deyarmin B, Kane JL, Valente AL, van Laar R, Gallagher C, Shriver CD, Ellsworth RE. "Effect of ASCO/CAP guidelines for determining ER status on molecular subtype." *AnnSurgOncol*, 2013 Jan;20(1):87-93, doi: 10.1245/s 10434-12-2588-8. Epub 2012 Aug 9.

Rummel S, Varner E, Shriver CD, Ellsworth RE. "Evaluation of BRCA1 mutations in an unselected patient population with triple negative breast cancer." *Breast cancer Res Treat* (2013) 137:119-125. doi 10.1007/s105-49-012-2348-2. Epub 2012 Nov 29.

Barault L, Ellsworth RE, Harris HR, Valente AL, Shriver CD, Michels KB. Leukocyte DNA as Surrogate for the Evaluation of Imprinted Loci Methylation in mammary tissue DNA. *PLOS ONE*, Vol 8, Issue 2, e55896, Feb 2013.

V. Conclusions

- On February 21, 2012 The Comprehensive Cancer Center at the Walter Reed National Military Medical Center submitted an application for designation by the Military Health System (MHS) Center of Excellence Oversight Board as a MHS Comprehensive Cancer Center of Excellence under the direction of Colonel Craig D. Shriver, MC, USA
- The CBCP has leased space at 11300 Rockville Pike, Suite 904. This space was leased for our Pathology team to have access to a computer network not behind the WRNMMC firewall.
- A COE Oversight Board meeting occurred on May 22, 2012. The WRNMMC Cancer Center received Center of Excellence status and is the only so designated Cancer Center in the DoD.
- On December 3, 2012 the cancer center at WRNMMC was named and dedicated to the memory of Congressman John P. Murtha.
- On December 18, 2012 the 50,000 specimen was ceremoniously placed in the freezer at Windber Research Institute.

VI. Appendices

a. Staff and role from 2 April 2012 – 31 March 2013

Last Name	First Name	Role
Shriver	Craig	Principal Investigator
Basham	Janice	Licensed Practical Nurse
Boone	Jaime	Program Manager/Budget Analyst
Bronfman	Eileen	Administrative Director
Campbell	Jamie Leigh	Pathology Assistant
Chestang	Allan	Data Manager
Cordes	Rosemarie	Research Nurse
Cronin	Kerri	Administrative Assistant
Eckhauser	Peggy Lee	Research Nurse
Ellsworth	Rachael	Director of Translational Genomics
Hilton	Karrie	Research Nurse
Hooke	Jeffrey	Head of Pathology
Kelly	Kay	Research Protocol Coordinator
Kovatch	Albert	Scientist
Means	Marilyn	Lab Tech
Miskovsky	Vicki Jones	Admin Reviewer CCC Protocols
Nielsen	Deborah	Research Nurse

Patterson	Carol	Medical Assistant
Simmons	Stephanie	Research Nurse
Tracey	Dianne	Administrative Assistant/Office Mngr.
Vilakazi	Patricia	Research Nurse
Wareham	Janet	Pathologist Assistant
Weiss	Raymond	Physician
Williamson	Eric	Clinic Administrator
Yambaka	Baredu	Receptionist/Research Assistant
Zhu	Kangmin	Epidemiologist
Zingmark	Rebecca	Histology Tech